New Primary Neoplasms of the Central Nervous System in Survivors of Childhood Cancer: a Report From the Childhood Cancer Survivor Study

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Background: **Subsequent primary neoplasms of the central nervous system (CNS) have frequently been described as late events following childhood leukemia and brain tumors. However, the details of the dose–response relationships, the expression of excess risk over time, and the modifying effects of other host and treatment factors have not been well defined.** ***Methods:*** **Subsequent primary neoplasms of the CNS occurring within a cohort of 14 361 5-year survivors of childhood cancers were ascertained. Each patient was matched with four control subjects by age, sex, and time since original cancer diagnosis. Tumor site–specific radiation dosimetry was performed, and chemotherapy information was abstracted from medical records. Conditional logistic regression was used to estimate odds ratios (ORs), to calculate 95% confidence intervals (CIs), and to model the excess relative risk (ERR) as a function of radiation dose and host factors. For subsequent gliomas, standardized incidence ratios (SIRs) and excess absolute risks (EARs) were calculated based on Surveillance, Epidemiology, and End Results data.** ***Results:*** **Subsequent CNS primary neoplasms were identified in 116 individuals. Gliomas (n = 40) occurred a median of 9 years from original diagnosis; for meningiomas (n = 66), it was 17 years. Radiation exposure was associated with increased risk of subsequent glioma (OR = 6.78, 95% CI = 1.54 to 29.7) and meningioma (OR = 9.94, 95% CI = 2.17 to 45.6). The dose response for the excess relative risk was linear (for glioma, slope = 0.33 [95% CI = 0.07 to 1.71] per Gy, and for meningioma, slope = 1.06 [95% CI = 0.21 to 8.15] per Gy). For glioma, the ERR/Gy was highest among children exposed at less than 5 years of age. After adjustment for radiation dose, neither original cancer diagnosis nor chemotherapy was associated with risk. The overall SIR for glioma was 8.7, and the EAR was 19.3 per 10 000 person-years.** ***Conclusions:*** **Exposure to radiation therapy is the most important risk factor for the development of a new CNS tumor in survivors of childhood cancers. The higher risk of subsequent glioma in children irradiated at a very young age may reflect greater susceptibility of the developing brain to radiation. [J Natl Cancer Inst 2006;98:1528–37]**

The development of a new primary neoplasm has long been recognized as a possible late effect of curative therapy for an original childhood cancer *(1)*. Second and subsequent primary neoplasms have been reported to be increased among survivors of virtually all types of childhood cancer *(2)*; however, the risk varies widely by type of second neoplasm, the original cancer diagnosis, age at first cancer diagnosis, and primary cancer therapy *(3–6)*.

Among the new primary neoplasms reported in childhood cancer survivors, tumors of the central nervous system (CNS) are especially devastating. Malignant CNS tumors are fatal in a high proportion of patients, and even nonfatal cancers and benign tumors often have lasting health effects. New primary neoplasms of the CNS (hereafter referred to as subsequent neoplasms of the CNS) were among the earliest of all reported subsequent neoplasms *(5)*. Since that time, numerous investigators have reported the increased occurrence of subsequent primary CNS tumors of different histologies following a variety of primary childhood cancers *(2,4,7–13)*. Children who received therapeutic or prophylactic radiation to the CNS appear to be at greatest risk; however, the magnitude of risks for different histologic types of CNS tumor, the details of the dose–response relationships, the expression of excess risk over time, and the modification of those relationships by other host and treatment factors have not been well defined.

The Childhood Cancer Survivor Study (CCSS) is a large, retrospective cohort study of more than 14 000 5-year survivors of childhood cancer *(14)* that was constructed to allow for the quantification of the incidence of late effects of childhood cancer and its treatment. We conducted a nested case–control study of subsequent primary neoplasms of the CNS in this study population to characterize more precisely the risk of CNS tumors among long-term survivors of childhood cancer. This analysis also included the reconstruction of radiation dose to the site of the CNS tumor to allow detailed investigation of dose–response relationships.

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See "Notes" following "References."

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Subjects and Methods

Identification and Enrollment of the CCSS Cohort

The CCSS study population is a retrospective cohort constructed from the rosters of all children and adolescents treated for childhood cancer at any of the 26 collaborating institutions in the United States or Canada. Individuals who met the following criteria were eligible: diagnosis of cancer and initial treatment at one of the collaborating CCSS centers between January 1, 1970, and December 31, 1986; diagnosis of cancer before 21 years of age; and survival at least 5 years after a primary diagnosis of leukemia, CNS cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, kidney tumor, neuroblastoma, soft tissue sarcoma, or bone sarcoma. Medical records for each potential participant were reviewed individually to determine eligibility. The CCSS protocol and contact documents were reviewed and approved by the Human Subjects Committee at each participating institution. The study design and the cohort have been described previously *(14)*.

Participants are those childhood cancer patients for whom baseline data were collected from respondents (or parents of those under age 18) using self-administered questionnaires or telephone interviews. Information collected included demographic data, medication usage, physician-diagnosed medical conditions, pregnancy occurrence and outcomes, and health-related behaviors, in addition to information regarding recurrence of the primary cancer or a new diagnosis of cancer or benign neoplasm. In situations in which the child had survived 5 years and subsequently died, information was obtained from a family member, usually a parent. The current analysis is based on data collected through December 31, 2001.

Of the 20 720 patients determined to be eligible for the CCSS, 6359 were excluded. Those excluded were eligible subjects who were determined to be lost to follow-up after rigorous tracing efforts [3026 (14.6%)], those who refused to participate in the study [3189 (15.4%)], and those who were located only recently and asked to consider participation in the CCSS [144 (6.9%)]. Thus, data were available for the current analysis on a total of 14 361 individuals.

Cancer Treatment Information

Therapeutic exposures were ascertained through review of the medical record of each study participant by trained data abstractors using a standardized protocol. Data collected included the dates of initiation and cessation of treatment with all chemotherapeutic agents, as well as cumulative doses and routes of administration of 28 specific agents. Information on all surgical procedures was also collected and coded, and radiation therapy data were forwarded to the CCSS Radiation Data Center at The University of Texas M. D. Anderson Cancer Center for coding and dosimetry assessment.

Ascertainment of New Primary CNS Tumor Case Patients and Selection of Control Subjects

Second and subsequent primary cancers and benign neoplasms were initially ascertained through self-report via the baseline and first follow-up questionnaire. Case patients were also ascertained through periodic searches of the National Death Index and reporting by next of kin. All positive responses were screened, and those representing likely or possible second primary tumors were forwarded to the CCSS Pathology Center (Columbus, OH) for verification. A request for a copy of the pathology report was made to the institution of record, and the CCSS pathologist reviewed all pathology reports of possible second cancers. In selected instances (e.g., glioma following other glial tumor), reports of the initial diagnosis were also reviewed. If the pathology report could not be obtained, the patient and/or parent questionnaire response, death certificate, and/or other institutional records were reviewed to determine the presence of a subsequent neoplasm. A trained nosologist coded all identified subsequent neoplasms to International Classification of Diseases for Oncology (ICD-O)-2 codes. Case patients were defined as those members of the cohort who were found to have a subsequent neoplasm of the CNS (including meninges) of any histology or behavior (ICD-O fifth digit code 0–3). Subsequent CNS tumors were subgrouped into four categories: meningioma (ICD-O-2 codes 9530–9539), glioma and other neuroepitheliomatous neoplasms (ICD-O-2 codes 9380–9523, excluding codes 9470–9473), primitive neuroectodermal tumor (ICD-O codes 9470–9473), and other or unclassified CNS neoplasms.

Four individually matched control subjects were selected randomly from the cohort for each case patient. Control subjects were matched to case patients by age at original cancer diagnosis (±2 years), elapsed time since original cancer diagnosis (at least that of case patient), and sex. We elected not to match case patients and control subjects on type and year of diagnosis of first cancer because of concerns about possible overmatching.

Tumor Localization and Radiation Dosimetry

All available records for each case patient were reviewed by a pediatric oncologist (J. Neglia) to determine as precisely as possible the location of the subsequent CNS neoplasm. Records reviewed included operative notes, pathology reports, radiology reports, and any correspondence in the available medical record relevant to the CNS neoplasm. Original imaging studies were not obtained. Based on these records, the location of the CNS tumor was drawn on a three-dimensional grid map that included eight axial sections of the brain containing a total of 282 unique points. Points were evenly spaced on the grid. The spacing between points varied from 1.3 to 2 cm, depending on the age of the patient, with smaller distances for younger ages. Spinal tumors were defined by vertebral level. We located one calculation point in the center of each vertebra and five in the sacrum.

The radiation therapy records for all case patients and control subjects were reviewed to determine therapy details. Institutions were contacted for missing treatment information when necessary. Radiotherapy information abstracted included dates of therapy, beam energy, field size, field location, and total dose to each field, given either prophylactically or as treatment of recognized disease. Age of the child at the time of therapy was used to determine height and, subsequently, distance from treatment field to CNS tumor site. The overall approach in determining organ doses in children treated with radiation dose is detailed in a separate report *(15)*. For each case patient, the site of the CNS tumor was characterized by points within the boundaries of the areas drawn on the grid maps. For each set of case patient and control subjects,

doses to the selected subset of points were averaged to estimate the dose to the region. Minimum and maximum doses within the regions were also reported. For the 11 case patients for whom there was no information on the tumor location within the CNS, the tumor was assumed to be in the brain. An average dose to the brain was reported for these subjects and the 44 matched control subjects.

Statistical Analysis

This analysis had four primary objectives: 1) to estimate histology-specific CNS tumor relative risk associated with radiotherapy, with any chemotherapy, and with alkylating agents, anthracyclines, epipodophyllotoxins, platinum agents, or antimetabolites specifically; 2) to describe the radiation dose–response relationship; 3) to assess whether the dose–response relationship depends on host characteristics, such as sex, age at first cancer diagnosis, time since first cancer, and original diagnosis group; and 4) to compare the incidence of new primary CNS cancers in the CCSS cohort with that in the US general population.

A cutoff date was defined for all participants. For case patients, the cutoff date was same as the date of CNS tumor diagnosis, whereas for control subjects, it was the first diagnosis date plus the length of follow-up of the matched case patient. Time-dependent variables were then coded according to their status at the subject's cutoff date. Radiation dose, however, was calculated by summing every dose from the first to last treatment given on or before a date 5 years before the cutoff date. Radiation doses given within 5 years before the cutoff date were not included to account for the minimum latency of most radiation-related solid cancers.

Conditional logistic regression (PROC PHREG of SAS version 9) was used to estimate odds ratios (ORs) and to calculate 95% confidence intervals (CIs). Analyses were adjusted for type of first cancer (leukemia, CNS cancer, other). Dose–response models and effect modification were evaluated using PECAN *(16,17)*, a program for conditional regression that allows for modeling of the excess relative risk (ERR). The excess relative risk equals the relative risk minus 1.0. Radiation dose–response models that were considered were simplifications of the general model ERR = $(B_1D + B_2D^2)\exp(B_3D + B_4D^2)$, in which D is dose and B_1–B_4 are regression coefficients. The exponential term allows for the effects of cell killing at high doses. The model ERR = B_1D corresponds to a linear dose–response relationship, and in this situation B_1 equals the ERR/Gy. We evaluated possible modification of B_1 under this model by sex, age at diagnosis of first cancer, attained age, and time since first cancer. Statistical significance was assessed based on likelihood ratio tests (two-sided).

Standardized incidence ratios (SIRs) and excess absolute risks (EARs) for glioma were calculated using age-, sex- and calendar year–specific rates from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute (NCI) for the subset of patients with malignant gliomas (ICD-O behavior code of 3). Standardized incidence ratios were calculated as the ratios of observed to expected numbers of case patients. Excess absolute risks were calculated as the difference between the numbers of observed and expected events divided by the number of person-years and expressed per 10 000 person-years. General population incidence rates were not available for meningioma.

Results

Characteristics of the Case Patients and Control Subjects

Subsequent primary CNS tumors were identified among 116 members of the CCSS cohort as of January 1, 2002. The most common subsequent CNS neoplasm was meningioma (n = 66), followed by glioma (n = 40), primitive neuroectodermal tumor (n = 6), and CNS lymphoma (n = 1); there were three tumors of unknown histology. In four instances the pathology report was unavailable. In three of these the CNS tumor was referenced in medical correspondence; the fourth was assigned based on parental response in the questionnaire. The gliomas included glioblastomas (n = 10), anaplastic astrocytomas (n = 9), other malignant gliomas (n = 10), gliosarcomas (n = 1), oligodendrogliomas (n = 4, two were anaplastic), and low-grade neoplasms (juvenile pilocytic astrocytoma [n = 2], fibrillary astrocytoma, myopapillary ependymoma, ganglioglioma, giant cell astrocytoma [one of each]). Three of the 66 meningiomas were recognized as malignant meningiomas. Other specified meningioma subtypes included meningotheliomatous (n = 5), fibrous (n = 4), and transitional (n = 4). Six case patients had subsequent CNS tumors in the spine.

Characteristics of the case patients and matched control subjects are shown in Table 1. By design, case patients and control subjects were matched by age at primary cancer, sex, and time since original cancer diagnosis. A higher percentage of case patients than control subjects had leukemia or CNS cancer as their first cancer. More leukemia patients subsequently developed gliomas than meningiomas, and more CNS cancer patients had subsequent meningiomas than gliomas. Five case patients and nine control subjects had new primary non-CNS neoplasms diagnosed between the date of diagnosis of their initial cancer and the cutoff date. Radiation doses for intervening cancers were included in the dosimetry if they occurred 5 or more years before the date of new CNS cancer.

Subsequent CNS tumors occurred from 5 to 28 years after the date of the original cancer diagnosis (Table 1). Patients with tumors that were diagnosed within the first 5 years after diagnosis of the first cancer were excluded because of the eligibility requirement that members of the cohort must have survived for at least 5 years. The median time to the occurrence of CNS tumor from original cancer diagnosis was 14 years overall, 9 years for gliomas, and 17 years for meningiomas. The majority of subsequent gliomas (21 of 40 [52.5%]) occurred during the initial 5 years of follow-up (5–9 years from cancer diagnosis); only four were diagnosed after 15 years (Table 1, Fig. 1). Conversely, meningiomas tended to appear later, with 71.2% (n = 47) diagnosed 15 or more years from the primary cancer diagnosis and with no sign of a decline in the numbers of new case patients with increasing time (Table 1, Fig. 1). The median age at diagnosis of the new CNS tumor was 20.5 years (15.0 for glioma and 25.5 for meningioma); 70% of gliomas were diagnosed before age 20, whereas 74% of meningiomas were diagnosed after age 20.

Risk of Glioma Relative to General Population

Within the cohort, 40 gliomas occurred compared with an expected 4.62 (SIR = 8.66, 95% CI = 6.24 to 11.6) (Table 2). Standardized incidence ratios were similar for males and females (9.64 and 7.28, respectively) but did vary by time from initial cancer diagnosis, age at original diagnosis, treatment era (1970–1974, 1975–1979, 1980–1986), cancer treatment, and original

Table 1. Characteristics of patients in the Childhood Cancer Survivors Study cohort with brain tumor as second (or subsequent) cancer and matched control subjects*

Characteristic	No. (%)			
	Glioma (n = 40)	Meningioma (n = 66)	All case patients (n = 116)	All control subjects (n = 464)
Original diagnosis				
Leukemia	24 (60.0)	31 (47.0)	60 (51.7)	173 (37.3)
CNS tumor	8 (20.0)	27 (40.9)	36 (31.0)	51 (11.0)
Hodgkin disease	2 (5.0)	1 (1.5)	5 (8.8)	52 (11.2)
Non-Hodgkin lymphoma	2 (5.0)	3 (4.55)	5 (4.3)	27 (5.8)
Kidney (Wilms)	0 (0.0)	0 (0.0)	1 (0.9)	41 (8.8)
Neuroblastoma	2 (5.0)	0 (0.0)	2 (1.7)	51 (11.0)
Soft tissue sarcoma	1 (2.5)	3 (4.55)	5 (4.3)	38 (8.2)
Bone tumor	1 (2.5)	1 (1.5)	2 (1.7)	31 (6.7)
Age at diagnosis of first cancer, y				
0–4	25 (62.5)	30 (45.4)	62 (53.45)	258 (55.6)
5–9	7 (17.5)	20 (30.3)	28 (24.1)	100 (21.6)
10–14	6 (15.0)	10 (15.2)	18 (15.5)	71 (15.3)
15–20	2 (5.0)	6 (9.1)	8 (6.9)	35 (7.5)
Age at diagnosis of subsequent CNS tumor, y				
5–9	8 (20.0)	2 (3.0)	11 (9.5)	N/A
10–14	11 (27.5)	2 (3.0)	18 (15.5)	N/A
15–19	9 (22.5)	13 (19.7)	23 (19.8)	N/A
20–24	7 (17.5)	14 (21.2)	21 (18.1)	N/A
25–29	3 (7.5)	21 (31.8)	26 (22.4)	N/A
30–34	2 (5.0)	10 (15.2)	13 (11.2)	N/A
35–40	0 (0.0)	4 (6.1)	4 (3.5)	N/A
Year of diagnosis of first cancer				
1970–1974	5 (12.5)	23 (34.8)	31 (26.7)	171 (36.9)
1975–1979	11 (27.5)	27 (40.9)	40 (34.5)	162 (34.9)
1980–1986	24 (60.0)	16 (24.2)	45 (38.8)	131 (28.2)
Time since diagnosis of first cancer, y				
5–9	21 (52.5)	5 (7.6)	31 (26.7)	124 (26.7)
10–14	15 (37.5)	14 (21.2)	33 (28.5)	132 (28.5)
≥15	4 (10.0)	47 (71.2)	52 (44.8)	208 (44.8)
Sex				
Male	26 (65.0)	33 (50.0)	62 (53.4)	248 (53.4)
Female	14 (35.0)	33 (50.0)	54 (46.6)	216 (46.6)
Race				
White	33 (82.5)	63 (95.5)	105 (90.5)	389 (83.8)
Black	3 (7.5)	1 (1.5)	4 (3.5)	16 (3.5)
Other	4 (10.0)	2 (3.0)	7 (6.0)	57 (12.3)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
Treatment for original childhood cancer				
Surgery only	1 (2.5)	0 (0)	1 (0.9)	30 (6.5)
Radiation therapy only	1 (2.5)	0 (0)	1 (0.9)	0 (0.0)
Chemotherapy only	1 (2.5)	0 (0)	1 (0.9)	26 (5.6)
Surgery + radiation therapy	6 (15.0)	16 (24.2)	23 (19.8)	48 (10.3)
Surgery + chemotherapy	0 (0)	2 (3.03)	3 (2.6)	64 (13.8)
Radiation therapy + chemotherapy	6 (15.0)	19 (28.8)	27 (23.3)	63 (13.6)
Surgery + radiation therapy + chemotherapy	25 (62.5)	25 (37.9)	56 (48.3)	198 (42.7)
Unknown	0 (0)	4 (6.06)	4 (3.45)	35 (7.5)
Treatment for recurrence of primary cancer before subsequent CNS tumor (or date of censoring)				
Yes/before cutoff	4 (10.0)	6 (9.1)	12 (10.3)	39 (8.4)
Yes/after cutoff	0 (0)	3 (4.6)	4 (3.4)	3 (0.6)
Yes/do not know the date	0 (0)	0 (0)	0 (0)	8 (1.7)
No	36 (90.0)	55 (83.3)	98 (84.5)	413 (89.0)
Unknown	0 (0)	2 (3.0)	2 (1.7)	1 (0.2)

*CNS = central nervous system; N/A = not applicable.

cancer diagnosis. Standardized incidence ratios were greatest for children who were younger than 5 years at their original diagnosis (SIR = 14.5), children within the first 15 years of follow-up (years 5–9, SIR = 13.9, and years 10–14, SIR = 11.2), and children treated during the last period of subject accrual (for diagnosis during 1980–1986, SIR = 12.7). Children whose treatment regimens included radiotherapy were at highest risk (for combination radiation and chemotherapy, SIR = 12.9, and for radiation alone, SIR = 11.2) as were those with a primary diagnosis of either leukemia (SIR = 16.9) or CNS tumor (SIR = 14.2).

Excess absolute risk for secondary glioma was 19.3 per 10 000 years follow-up (Table 2). Excess absolute risk was increased for both males and females and was highest during the first 15 years following diagnosis, falling considerably after that. Similarly, excess absolute risk was highest for children diagnosed at youngest ages (ages 0–4 years, EAR = 31.95). Radiation

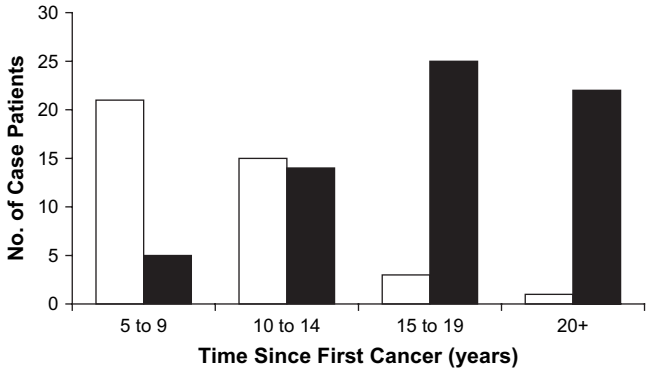

Fig. 1. Time to occurrence of subsequent glioma or meningioma in the Childhood Cancer Survivor Study cohort from original cancer diagnosis (**open bars**, gliomas; **closed bars**, meningiomas).

therapy alone or in combination with chemotherapy was associated with excess absolute risks of 27.5 and 29.6, respectively. The excess absolute risk for patients not treated with radiotherapy was not statistically significantly increased. Children who were originally diagnosed with leukemia or CNS tumors had the most elevated excess absolute risks in the cohort.

Detailed Therapy-Related Risk Factors for CNS Tumors

We next determined the odds ratios for the occurrence of a CNS tumor following exposure to radiotherapy or chemotherapy (Table 3). One hundred ten of the case patients (95.6%) and 322 of the control subjects (72.7%) had received radiation therapy for treatment of the primary cancer. In one case patient and 24 control subjects, the quality of the medical records available did not permit a radiation exposure assignment. After adjustment for original diagnosis, any exposure to radiation therapy was associated with a statistically significantly increased risks for the development of subsequent glioma (OR = 6.78, 95% CI = 1.54 to 29.7), meningioma (OR = 9.94, 95% CI = 2.17 to 45.6), and all CNS tumors combined (OR = 7.07, 95% CI = 2.76 to 18.1); however, these odds ratios are based on just two nonexposed glioma case patients and two nonexposed meningioma case patients.

Highly statistically significant radiation dose–response relationships ($P<.001$) were observed for all CNS tumors combined as well as for glioma and meningioma individually (Table 4, Fig. 2). Because of the small number of nonirradiated case patients, we used dose less than 1 Gy as the reference category. The odds ratios for subsequent glioma rose sharply across the radiation categories and peaked at 21-fold for doses of 30–44.9 Gy. There were no case patients of either type in the 1–9.9 Gy range. Odds ratios were higher across all other categories of radiation dose for meningioma, peaking at 96.3, in the 30–44.9 Gy dose category. The excess relative risk per Gy, equal to the slope of the linear dose–response function, was 0.33 (95% CI = 0.07 to 1.71) per Gy for glioma, 1.06 (95% CI = 0.21 to 8.15) per Gy for meningioma, and 0.69 (95% CI = 0.25 to 2.23) per Gy for all CNS tumors. Addition of either quadratic or exponential terms in dose to allow for possible upward or downward curvature in the

Table 2. Standardized incidence ratios (SIRs) and excess absolute risks (EARs) for glioma in the Childhood Cancer Survivor Study cohort

Category	No. observed	No. expected	SIR (95% CI)	EAR (95% CI)*
Overall	40	4.62	8.66 (6.24 to 11.6)	19.3 (13.2 to 26.8)
Sex				
Male	26	2.70	9.64 (6.39 to 13.8)	24.5 (15.3 to 36.4)
Female	14	1.92	7.28 (4.10 to 11.8)	13.7 (6.79 to 23.6)
Age at original diagnosis, y				
0–4	25	1.72	14.5 (9.56 to 21.0)	31.9 (20.2 to 47.2)
5–9	7	0.94	7.48 (3.21 to 14.5)	15.0 (5.11 to 31.1)
10–14	6	0.96	6.24 (2.48 to 12.6)	13.6 (3.83 to 30.2)
15–20	2	1.00	1.99 (0.33 to 6.16)	3.07 (−2.06 to 15.9)
Years from original diagnosis				
5–9	21	1.51	13.9 (8.79 to 20.8)	30.8 (18.5 to 47.0)
10–14	15	1.34	11.2 (6.43 to 17.8)	23.9 (12.8 to 39.5)
15–19	3	0.99	3.04 (0.76 to 7.88)	5.25 (−0.63 to 17.7)
≥20	1	0.78	1.28 (0.07 to 5.63)	0.90 (−3.00 to 14.9)
Calendar year of treatment				
1970–1974	5	1.24	4.04 (1.45 to 8.69)	8.05 (1.19 to 20.3)
1975–1979	11	1.49	7.38 (3.83 to 12.6)	15.9 (7.06 to 29.0)
1980–1986	24	1.89	12.7 (8.26 to 18.4)	28.9 (18.0 to 43.2)
Treatment characteristics				
Radiation + chemotherapy	31	2.40	12.9 (8.88 to 18.0)	29.6 (19.6 to 42.2)
Radiation only	7	0.63	11.2 (4.80 to 21.6)	27.5 (10.3 to 55.6)
Chemotherapy only	1	0.99	1.01 (0.06 to 4.46)	0.03 (−2.36 to 8.66)
No radiation or chemotherapy	1	0.34	2.90 (0.17 to 12.8)	4.96 (−2.17 to 30.7)
Original diagnosis				
Leukemia	24	1.42	16.9 (11.0 to 24.7)	38.0 (23.9 to 56.3)
CNS† tumor	8	0.56	14.2 (6.51 to 26.5)	33.0 (13.7 to 63.5)
Hodgkin disease	2	0.74	2.70 (0.45 to 8.34)	4.81 (−1.56 to 20.8)
Non-Hodgkin lymphoma	2	0.37	5.40 (0.90 to 16.7)	11.8 (−0.27 to 42.2)
Kidney tumor (Wilms)	0	0.38	0.00 (0.00 to 7.96)	−2.32 (−2.32 to 16.2)
Neuroblastoma	2	0.31	6.48 (1.08 to 20.0)	13.1 (0.19 to 45.6)
Soft tissue sarcoma	1	0.43	2.34 (0.13 to 10.30)	3.45 (−2.23 to 23.9)
Bone cancer	1	0.42	2.39 (0.14 to 10.5)	3.78 (−2.36 to 25.9)

*EARs are per 10 000 person-years.

†CNS = central nervous system.

Table 3. Exposures and adjusted odds ratios of CNS subsequent neoplasm by type of treatment for initial cancer*

Treatment	Glioma			Meningioma			All CNS tumors†		
	No. of case patients	No. of control subjects	OR (95% CI)	No. of case patients	No. of control subjects	OR (95% CI)	No. of case patients	No. of control subjects	OR (95% CI)
XRT (no adj)									
No	2	48	1.0 (referent)	2	61	1.0 (referent)	5	120	1.0 (referent)
Yes	38	102	6.78 (1.54 to 29.7)	63	189	9.94 (2.17 to 45.6)	110	320	7.07 (2.76 to 18.1)
Unk	0	10	0.0 (0.00 to 12.5)	1	14	1.95 (0.15 to 25.7)	1	24	0.78 (0.08 to 7.31)
Chemo									
No	8	31	1.0 (referent)	16	42	1.0 (referent)	25	78	1.0 (referent)
Yes	32	116	0.66 (0.15 to 2.90)	46	202	1.40 (0.29 to 6.79)	87	352	0.80 (0.31 to 2.03)
Unk	0	13	0.00 (0.00 to 0.62)	4	20	1.01 (0.15 to 6.99)	4	34	0.27 (0.06 to 1.11)
Alk Agent									
No	19	69	1.0 (referent)	37	126	1.0 (referent)	59	212	1.0 (referent)
Yes	21	78	1.10 (0.45 to 2.66)	25	118	0.85 (0.34 to 2.09)	53	218	1.03 (0.58 to 1.83)
Unk	0	13	0.00 (0.00 to 0.76)	4	20	0.69 (0.16 to 2.96)	4	34	0.33 (0.09 to 1.17)
Anthracycline									
No	26	89	1.0 (referent)	56	178	1.0 (referent)	90	298	1.0 (referent)
Yes	14	58	0.90 (0.37 to 2.20)	6	66	0.33 (0.11 to 1.04)	22	132	0.63 (0.34 to 1.19)
Unk	0	13	0.00 (0.00 to 0.67)	4	20	0.54 (0.13 to 2.24)	4	34	0.28 (0.08 to 0.97)
Epipodoph									
No	33	139	1.0 (referent)	58	237	1.0 (referent)	100	413	1.0 (referent)
Yes	7	8	2.43 (0.63 to 9.32)	4	7	2.19 (0.29 to 16.7)	12	17	1.78 (0.62 to 5.14)
Unk	0	13	0.00 (0.00 to 0.62)	4	20	0.78 (0.20 to 3.11)	4	34	0.32 (0.09 to 1.10)
Platinum									
No	38	141	1.0 (referent)	57	238	1.0 (referent)	104	414	1.0 (referent)
Yes	2	6	1.99 (0.20 to 19.8)	5	6	3.07 (0.17 to 55.7)	8	16	1.15 (0.27 to 4.91)
Unk	0	13	0.00 (0.00 to 0.69)	4	20	0.78 (0.20 to 3.08)	4	34	0.32 (0.09 to 1.10)
6MP or 6TG									
No	15	88	1.0 (referent)	30	147	1.0 (referent)	50	257	1.0 (referent)
Yes	25	59	0.75 (0.13 to 4.45)	32	97	1.37 (0.26 to 7.21)	62	173	1.00 (0.34 to 2.96)
Unk	0	13	0.00 (0.00 to 0.66)	4	20	0.88 (0.18 to 4.44)	4	34	0.32 (0.09 to 1.17)

*Adjusted by diagnosis group (leukemia, CNS, other); all chemotherapy data adjusted by radiation dose. Radiation dose categories: <1 Gy, 1–9.9 Gy, 10–19.9 Gy, 20–29.9 Gy, 30–44.9 Gy, ≥45 Gy, dose unknown. CNS = central nervous system; OR = odds ratio; CI = confidence interval; XRT = therapeutic radiation; adj = adjustment; unk = unknown; chemo = chemotherapy; alk = alkylating; epipodoph = epipodophyllotoxin; platinum = platinum agents (cisplatinum or carboplatinum); 6MP = 6-mercaptopurine; 6TG = 6-thioguanine.

†Total is greater than sum of gliomas and meningiomas because of inclusion of additional case patients and control subjects.

dose–response did not statistically significantly improve the fit of the linear model for either histologic subtype. The models that simultaneously included linear, quadratic, and exponential terms failed to converge and were therefore discarded.

After adjustment for radiation dose and original diagnosis, no statistically significant associations were seen between risk of second or subsequent CNS tumors and chemotherapy exposure overall or exposure to alkylating agents, anthracyclines, epipodophyllotoxins, platinum agents, or antimetabolites specifically (Table 3). There were non–statistically significant increases in the odds ratios for glioma associated with prior epipodophyllotoxin and platinum exposure. Antimetabolite exposure (6MP or 6TG) was not associated with an increased risk of glioma (OR = 0.75, 95% CI = 0.13 to 4.45). Statistically nonsignificant increases in odds ratios were observed among patients with meningioma who had prior epipodophyllotoxin or platinum exposure. With adjustment for radiation dose, type of first cancer was not statistically significantly associated with risk of subsequent CNS tumors.

Modification of Radiation Effect by Host Characteristics

In analyses of modification of radiation effect by host characteristics, the excess relative risk per Gy did not vary statistically significantly according to most of the factors considered (Table 5). For glioma, the ERR/Gy was not statistically different between males and females, the ERR/Gy was higher for persons exposed before age 5 than after age 5, and the ERR/Gy dropped nearly to zero among persons followed past age 25. The ERR/Gy for glioma was statistically significantly different from zero only for children irradiated before age 5 years. For meningioma, the ERR/Gy was higher for children irradiated when they were older than 5 years than for those irradiated at younger ages.

Discussion

To our knowledge, this is the largest study to date of subsequent CNS tumors among childhood cancer survivors for whom detailed treatment information is available. The subsequent neoplasms occurred from 5 to 28 years following the original cancer diagnosis and most commonly were meningiomas or glial tumors. Gliomas tended to occur earlier than meningiomas. Exposure to therapeutic radiation delivered for treatment of the original cancer was the most important risk factor by far for the occurrence of a CNS neoplasm. The risk of a CNS tumor was more than sevenfold higher among persons who were treated with radiation for their initial cancer than those who were not, and dose–response relationships were apparent for both glioma and meningioma. For doses in excess of 30 Gy, relative risks were of the order of 20 for glioma and 50–100 for meningioma. These very high relative risks reflect the rarity of these tumors at young ages among nonirradiated persons. Indeed, only four of 106 case patients with subsequent glioma or meningioma had not received radiation for their original cancer. In contrast, after

Table 4. Radiation dose response (adjusted by original diagnosis and excluding persons with unknown radiation dose)*

Treatment dose (Gy)		Glioma			Meningioma			All CNS tumors		
Interval	Mean†	No. of case patients	No. of control subjects	OR (95% CI)	No. of case patients	No. of control subjects	OR (95% CI)	No. of case patients	No. of control subjects	OR (95% CI)
<1	0.1	5	72	1.0 (referent)	2	115	1.0 (referent)	8	207	1.0 (referent)
1–9.9	1.9	0	5	0.00 (0.00 to 5.17)	0	8	0.00 (0.00 to 15.8)	0	14	0.00 (0.00 to 2.44)
10–19.9	16.9	9	16	7.61 (1.49 to 38.8)	4	14	12.0 (1.42 to 100.7)	13	32	9.71 (2.73 to 34.5)
20–29.9	23.9	11	20	6.68 (1.47 to 30.3)	26	52	21.6 (3.13 to 149.3)	40	74	13.4 (4.30 to 41.79)
30–44.9	38.6	4	4	21.0 (3.11 to 142.3)	13	3	96.3 (10.32 to 899.3)	21	10	50.0 (13.3 to 187.4)
>45	48.8	6	6	17.5 (2.86 to 107.5)	13	4	58.0 (6.02 to 559.0)	19	10	32.8 (8.38 to 128.3)
All doses		35	123		58	196		101	347	

*OR = odds ratio; CI = likelihood-based confidence interval; CNS = central nervous system.
†Mean dose among all control subjects.

adjustment for radiation dose, neither exposure to chemotherapy in aggregate nor exposure to specific classes of chemotherapeutic agents was statistically significantly associated with risk of CNS tumor.

Many other investigators have studied the occurrence of CNS tumors in survivors of childhood cancer. Second neoplasms of the CNS were included in the initial reports of the Late Effects Study Group *(5,18)*. Several investigations *(2,7,19,20)* have shown an excess of CNS tumors following a diagnosis of childhood acute lymphoblastic leukemia (ALL), with a strong link to previous radiotherapy. In one, a study conducted at the St Jude Children's Research Hospital *(2)*, the median time to development of a subsequent meningioma was much greater than that to the development of a subsequent glioma (19 years versus 9.1 years), a result similar to our data. All patients received prior radiation therapy. Young age was associated with risk of subsequent high-grade glioma but not with the occurrence of brain tumors overall. In other studies, children with ALL who were treated with contemporary therapy (most often without prophylactic cranial irradiation) have shown a marked decrease in brain tumor risk relative to children treated in earlier years *(19,20)*.

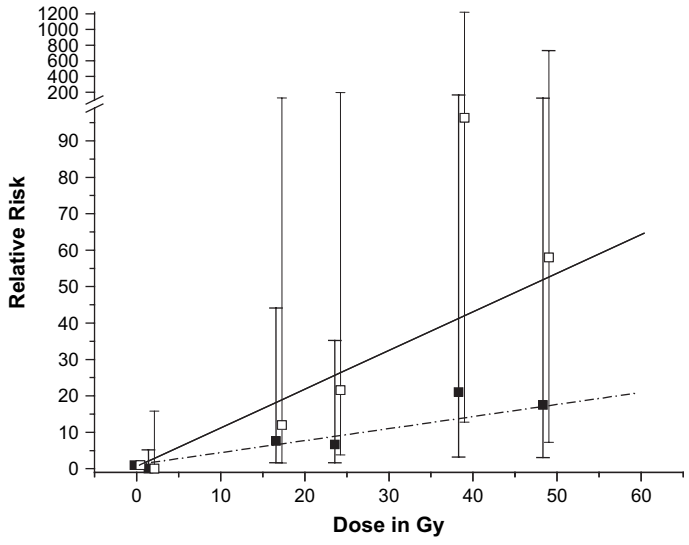

Fig. 2. Relative risk of subsequent glioma and meningioma within the Childhood Cancer Survivor Study cohort by radiation dose (**open boxes**, mean observed relative risk for meningioma; **closed boxes**, mean observed relative risk for glioma; **solid line**, fitted line for meninigioma risk; **hatched line**, fitted line for glioma risk). $P<.001$ (likelihood ratio test, two-sided).

Although most descriptions of CNS neoplasms occurring after treatment of a primary childhood cancer have shown an association of such subsequent neoplasms with prior radiation exposure, few have included investigation of radiation dose. A European study of 4400 children treated for a variety of childhood cancers (excluding leukemia) investigated 12 malignant (predominately glial) and 10 benign/unspecified tumors of the CNS *(10)*. A radiation dose–response relationship was seen for benign or unspecified tumors; however, no effect of dose was seen for malignant CNS tumors. The analysis showed little association between alkylating agents (the only chemotherapy considered) and CNS tumors.

Previous investigations have demonstrated clear associations between tumors of the CNS and radiotherapy during childhood for benign conditions as well as cancer. Among children who had been irradiated for treatment of *Tinea capitis*, Ron et al. *(21)* showed an association between radiation dose and the later occurrence of meningioma, glioma, and nerve sheath tumors. In that study, elevated risk was evident at doses as low as 1–2 Gy. An extended follow-up of this population *(22)* found an ERR/Gy of 1.98 for malignant CNS tumors and 4.63 for meningioma estimates that are higher than the overall estimates from the present study. As in the present study, the ERR/Gy for malignant CNS tumors was inversely associated with age at irradiation, whereas that for meningioma was not. However, the age distribution in the *Tinea* study was younger than in the CCSS. In a Swedish study of two cohorts of children treated with ionizing radiation for hemangiomas of the skin (combined N = 28 008), 40% of which were on the head or neck, children receiving radiotherapy at the youngest ages appeared to be at greatest risk of later developing an intracranial tumor *(23)*.

An analysis of the incidence of tumors of the nervous system with respect to radiation dose among survivors of atomic bomb explosions indicated increased risk at doses less than 1 sievert (Sv) *(24)* (1 Sv is equivalent to 1 Gy of therapeutic radiation). Dose–response relationships were linear, and excess risks were higher for persons exposed as children than as adults. The excess relative risk for meningioma among persons exposed at ages less than 20 years was 1.3 per Sv (95% CI = 0.01 to 4.5), which is similar to the value we observed (ERR = 1.06 per Gy) *(24)*. The dose–response was stronger for schwannoma than for glioma or meningioma. For all nervous system tumors other than schwannoma, the excess relative risk following childhood exposure in the atomic bomb cohort was 1.2 per Sv. The excess relative risk for glioma (all ages at exposure) was 0.56 per Sv (95% CI = −0.2 to 2.0).

Table 5. Excess relative risk (ERR) of tumor per Gy of radiation, 95% confidence intervals (CIs), and tests for heterogeneity in ERR by sex, age at irradiation (age at diagnosis of original cancer), and time since irradiation (diagnosis of original cancer)*

Characteristic	ERR (95% CI) per Gy of radiation		
	Glioma	Meningioma	All CNS† tumors
Total	0.33 (0.07 to 1.71)	1.06 (0.21 to 8.15)	0.69 (0.25 to 2.23)
P	<.001	<.001	<.001
Sex			
Male	0.48 (−0.48 to 1.43)	3.99‡	1.46 (0.32 to 3.32)
Female	0.23 (−0.25 to 0.71)	0.41 (−0.49 to 1.32)	0.41 (0.11 to 1.65)
$P_{heterogeneity}$	.58	.09	.20
Age at exposure, y			
<5	0.64 (0.12 to 5.66)	0.75 (0.11 to 6.59)	0.71 (0.22 to 2.67)
5–9	0.10 (−0.20 to 0.39)	1.99 (0.28 to 21.12)	0.78 (0.19 to 3.72)
10–20	0.15 (−0.23 to 0.52)	1.36 (0.10 to 30.69)	0.59 (0.12 to 3.60)
$P_{heterogeneity}$	.15	.16	.04
Years since first exposure			
5–9	0.45 (−0.46 to 1.36)	0.05 (−0.14 to 0.25)	0.39 (0.08 to 2.33)
10–14	0.18 (−0.20 to 0.56)	–‡	0.45 (0.10 to 2.97)
>15	–‡	–‡	2.07 (0.36 to 39.3)
$P_{heterogeneity}$			.10

*P values were determined using the likelihood ratio test (two-sided).

†CNS = central nervous system.

‡Model did not converge. Thus, reliable confidence intervals and/or maximum likelihood estimates were not obtained.

Although chemotherapy exposure alone has not been shown to be a risk factor for CNS tumors, one recent investigation *(25)* suggested that children with deficiency of the enzyme thiopurine methyltransferase (TPMT) may be at particularly high risk for CNS tumors when treated for ALL with a combination of radiotherapy and thiopurine chemotherapy. In that study, of six children with ALL who developed CNS cancers (five high-grade glioma, one primitive neuroectodermal tumor), three were noted to have polymorphisms of TPMT that were associated with decreased thiopurine catabolism. Although their conclusion was based on a small number of case patients, the authors suggested that children with ALL, especially those with TPMT polymorphisms, may be uniquely vulnerable to the tumorigenic effects of radiation while on thiopurine-based chemotherapy. In this study of CNS neoplasms in the CCSS cohort, we did not find any evidence of association between thiopurine exposure and CNS neoplasms in aggregate or CNS gliomas specifically. We did not, however, have access to the same level of patient-specific chemotherapy detail and did not include measurements of TPMT activity or other drug-metabolizing enzymes in our study.

In this study, the distribution of subsequent gliomas and meningiomas differed strikingly over time. The radiation-related increase in the incidence of glioma was apparent 5–10 years after exposure but largely disappeared after 15–20 years. By the time childhood cancer survivors reached their mid-20s, risk of glioma appeared to have dropped nearly to background levels. In contrast, the increase in meningioma took longer to appear and showed no signs of subsiding in the latest follow-up intervals. The later-appearing excess of meningioma may be related to the age-specific background incidence rates for this tumor. The decrease in the relative risk for glioma with time is in contrast with results for the atomic bomb survivors *(24)* and irradiated *T. capitis* patients *(22)*. If we failed to ascertain and include any case patient with glioma who died, it is possible that we underestimated risks; however, mechanisms were in place to include eligible deceased case patients.

These data present the largest and most complete assessment to date of the role of therapy and host characteristics pertinent to the development of new primary CNS tumors in long-term survivors of childhood cancer. The findings of this study are strengthened by several factors, including the large number of case patients, the long duration of follow-up, the detailed review of medical records for chemotherapy exposure, and the central review of all pathology reports. Most important, individual dosimetry was conducted for each case patient and control subject to assign a specific radiation dose to each tumor site. We have clearly shown a strong dose–response relationship between radiation dose and the occurrence of all CNS tumors; the association was especially strong for subsequent meningioma but was evident for glioma as well. The ERR/Gy for subsequent glioma was statistically significantly greater than zero only for ages at irradiation less than 5 years, which suggests that susceptibility to radiation-related brain cancer decreases as brain development nears completion. We did not find evidence of associations between CNS tumors and chemotherapy exposure or type of first cancer, once radiation dose was taken into account.

Despite the size and completeness of this analysis, there are some limitations to this investigation. In persons whose first cancer was a CNS glioma, it is difficult to determine whether a subsequent glioma represents recurrence of the original tumor, transformation of a low-grade CNS neoplasm to a high-grade tumor, or a new cancer. We based our determination of second CNS neoplasms on location, histology, time from diagnosis, and information provided by the treating institution. It is possible that we were overly restrictive about what we would accept as a new primary glioma after a first glioma and that we have underestimated the actual number of new glial tumors among patients with primary CNS tumors. We also a priori excluded any subsequent tumor occurring within the first 5 years following the original cancer diagnosis; thus, we are unable to comment on risk during that period of time. Another limitation is our reliance on self-report of both the occurrence of a subsequent neoplasm and comorbid conditions. The very limited information we had on pre-existing genetic disorders (most notably, neurofibromatosis type I) among study participants precluded meaningful analysis of these disorders as risk factors. The study had limited power to detect risks at doses less than 10 Gy because there were so few case patients who received a low dose of radiation at the site of the subsequent CNS tumor. Finally, despite the range of radiation dose delivered across study participants, there was a therapy-related clustering of dose by type of first cancer, with children treated for ALL characteristically receiving between 18 and 24 Gy and children with primary brain tumors receiving in excess of 40 cGy. This clustering may have masked possible disease–CNS neoplasm associations because of our inability to completely separate effects of the original disease and the radiation dose used for its therapy. Finally, care should be taken when generalizing these results to the population at large. The etiology of childhood cancer is largely unexplained, and children who

develop a primary cancer may intrinsically be at risk of a second tumor beyond the effects of chemotherapy or radiation.

This investigation makes clear the strong effect of radiation therapy on the occurrence of subsequent neoplasms of the CNS. Among children with cancer, the use of radiation therapy is never taken lightly, and it is administered only when necessary to successfully treat the primary cancer. Despite the risks associated with this therapeutic modality, the use of radiotherapy is justified in these settings because 60% of deaths among survivors of childhood cancer who are 5 or more years result from recurrence or progression of their original disease *(26)*. When radiation therapy is indicated, use of the minimum effective dose may reduce the risk of second CNS neoplasms occurring up to many years later. Finally, prolonged follow-up of all childhood cancer survivors, particularly those exposed to radiation, is crucial to the early detection of these tumors and should be considered part of the effective therapy of the primary disease.

Appendix

CCSS institutions and investigators include the following: University of California—San Francisco, CA: Robert Goldsby, MD (Institutional Principal Investigator), Arthur Ablin, MD (Former Institutional Principal Investigator); University of Alabama, Birmingham, AL: Roger Berkow, MD (Institutional Principal Investigator); International Epidemiology Institute, Rockville, MD: John Boice, ScD (Member CCSS Steering Committee); University of Washington, Seattle, WA: Norman Breslow, PhD (Member CCSS Steering Committee); UT-Southwestern Medical Center at Dallas, TX: Gail Tomlinson, MD (Institutional Principal Investigator), George R. 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